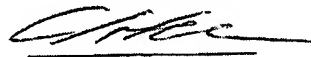


UNITED STATES PATENT AND TRADEMARK OFFICE

I, Charles Edward SITCH BA,

Managing Director of RWS Group Ltd UK Translation Division, of Europa House, Marsham Way, Gerrards Cross, Buckinghamshire, England declare;

1. That I am a citizen of the United Kingdom of Great Britain and Northern Ireland.
2. That the translator responsible for the attached translation is well acquainted with the German and English languages.
3. That the attached is, to the best of RWS Group Ltd knowledge and belief, a true translation into the English language of the accompanying copy of the specification filed with the application for a patent in Germany on December 12, 2002 under the number 102 58 008.1 and the official certificate attached thereto.
4. That I believe that all statements made herein of my own knowledge are true and that all statements made on information and belief are true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the patent application in the United States of America or any patent issuing thereon.



For and on behalf of RWS Group Ltd

The 8th day of April 2009

FEDERAL REPUBLIC OF GERMANY

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**Priority Certificate
for the filing of a Patent Application**

File Reference: 102 58 008.1

Filing date: 12 December 2002

Applicant/Proprietor: Aventis Pharma Deutschland GmbH
Frankfurt am Main/DE

Title: Novel heterocyclic fluoroglycoside derivatives, medicaments
containing these compounds, and the use thereof

IPC: C 07 H, A 61 K

The attached documents are a correct and accurate reproduction of the original
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Munich, 17 April 2003

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The President

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Agurks

Description

Novel heterocyclic fluoroglycoside derivatives, medicaments containing these compounds, and the use thereof

5

The invention relates to substituted heterocyclic fluoroglycoside derivatives, their physiologically tolerated salts and physiologically functional derivatives.

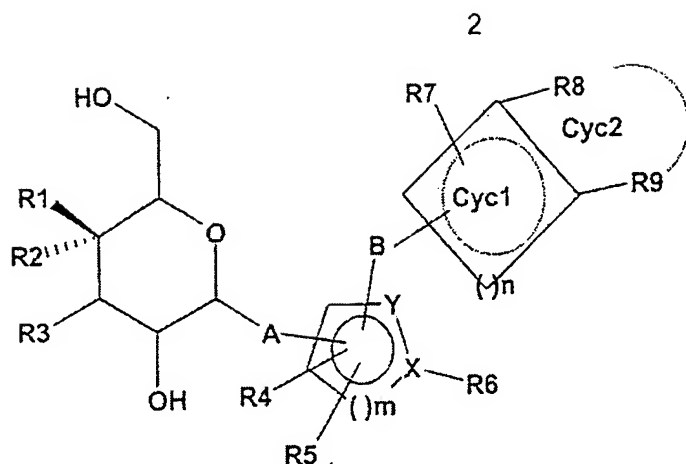
10 Several classes of substances having an SGLT effect have already been disclosed in the literature. The model for all these structures was the natural product phlorizin. From this were derived the following classes which are described in the property rights below:

- 15 - propiophenone glycosides of Tanabe (WO 0280936, WO 0280935, JP 2000080041 and EP 850948)
- 2-(glucopyranosyloxy)benzylbenzenes of Kissei (WO 0244192, WO 0228872 and WO 0168660)
- glucopyranosyloxypyrazoles of Kissei and Ajinomoto (WO 0268440, WO 0268439, WO 0236602 and WO 0116147)
- 20 - O-glycoside benzamides of Bristol-Myers Squibb (WO 0174835 and WO 0174834)
- and C-aryl glycosides of Bristol-Myers Squibb (WO 0127128 and US 2002137903).

25 All the known structures contain glucose as a very important structural element.

The invention was based on the object of providing novel compounds with which it is possible to prevent and treat type 1 and type 2 diabetes. We have now surprisingly found that aromatic fluoroglycoside derivatives
30 increase the effect on SGLT. These compounds are therefore particularly suitable for preventing and treating type 1 and type 2 diabetes.

The invention therefore relates to compounds of the formula I



in which the meanings are

- 5 R1, R2 OH, F or H or R1 and R2 = F;
- R3 OH or F, where one of the R1, R2, R3 radicals must be F;
- A O, NH, CH₂, S or a bond;
- 10 X O, S or optionally R6-substituted N, where Y must be CH
 when X is O or S;
- Y CH, N, O, S;
- 15 m a number 1 or 2;
- R4, R5 hydrogen, F, Cl, Br, I, OH, CF₃, NO₂, CN, COOH,
 CO(C₁-C₆)-alkyl, COO(C₁-C₆)-alkyl, CONH₂, CONH(C₁-C₆)-
20 alkyl, CON[(C₁-C₆)-alkyl]₂, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl,
 (C₂-C₆)-alkynyl, (C₁-C₆)-alkoxy, HO(C₁-C₆)-alkyl, (C₁-C₆)-
 alkoxy-(C₁-C₆)-alkyl, phenyl, benzyl, it being possible for one,
 more than one or all hydrogen(s) in the alkyl radicals to be
 replaced by fluorine;
- 25 SO₂-NH₂, SO₂NH(C₁-C₆)-alkyl, SO₂N[(C₁-C₆)-alkyl]₂,
 S-(C₁-C₆)-alkyl, S-(CH₂)₀-phenyl, SO-(C₁-C₆)-alkyl,
 SO-(CH₂)₀-phenyl, SO₂-(C₁-C₆)-alkyl, SO₂-(CH₂)₀-phenyl,
 where o can be 0-6, and the phenyl radical may be
 substituted up to twice by F, Cl, Br, OH, CF₃, NO₂, CN,
30 OCF₃, O-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl, NH₂;

- 5 NH₂, NH-(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)₂, NH(C₁-C₇)-acyl, phenyl, O-(CH₂)_o-phenyl, where o can be 0-6, where the phenyl ring may be substituted one to 3 times by F, Cl, Br, I, OH, CF₃, NO₂, CN, OCF₃, O-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl, NH₂, NH(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)₂, SO₂-CH₃, COOH, COO-(C₁-C₆)-alkyl, CONH₂;
- when X is S together with the C atoms carrying them phenyl;
- 10 R⁶ H, (C₁-C₆)-alkyl, (C₁-C₆)-alkenyl, (C₃-C₆)-cycloalkyl, or phenyl that may optionally be substituted by halogen or (C₁-C₄)-alkyl;
- B (C₀-C₁₅)-alkanediyl, it being possible for one or more C atoms in the alkanediyl radical to be replaced independently of one another by -O-, -(C=O)-, -CH=CH-, -C≡C-, -S-, 15 -CH(OH)-, -CHF-, -CF₂-, -(S=O)-, -(SO₂)-, -N((C₁-C₆)-alkyl)-, -N((C₁-C₆)-alkyl-phenyl)- or -NH-;
- n a number from 0 to 4;
- 20 Cyc1 a 3 to 7 membered saturated, partially saturated or unsaturated ring, where 1 C atom may be replaced by O, N or S;
- 25 R7, R8, R9 hydrogen, F, Cl, Br, I, OH, CF₃, NO₂, CN, COOH, COO(C₁-C₆)-alkyl, CO(C₁-C₄)-alkyl, CONH₂, CONH(C₁-C₆)-alkyl, CON[(C₁-C₆)-alkyl]₂, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₁-C₆)-alkoxy, (C₁-C₆)-alkyl-OH, (C₁-C₆)-alkoxy-(C₁-C₆)-alkyl, it being possible for one, more than one or all hydrogen(s) in the alkyl radicals to be replaced by 30 fluorine;
- SO₂-NH₂, SO₂NH(C₁-C₆)-alkyl, SO₂N[(C₁-C₆)-alkyl]₂, S-(C₁-C₆)-alkyl, S-(CH₂)_o-phenyl, SO-(C₁-C₆)-alkyl, SO-(CH₂)_o-phenyl, SO₂-(C₁-C₆)-alkyl, SO₂-(CH₂)_o-phenyl, 35 where o can be 0-6, and the phenyl radical may be substituted up to twice by F, Cl, Br, OH, CF₃, NO₂, CN, OCF₃, O-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl, NH₂; NH₂, NH-(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)₂, NH(C₁-C₇)-acyl,

phenyl, O-(CH₂)_o-phenyl, where o can be 0-6, where the phenyl ring may be substituted one to 3 times by F, Cl, Br, I, OH, CF₃, NO₂, CN, OCF₃, (C₁-C₈)-alkoxy, (C₁-C₆)-alkyl, NH₂, NH(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)₂, SO₂-CH₃, COOH, COO-(C₁-C₆)-alkyl, CONH₂;

or

R8 and R9 together with the C atoms carrying them a 5 to 7 membered, saturated, partially or completely unsaturated ring Cyc2, it being possible for 1 or 2 C atom(s) in the ring also to be replaced by N, O or S, and Cyc2 may optionally be substituted by (C₁-C₆)-alkyl, (C₂-C₅)-alkenyl, (C₂-C₅)-alkynyl, where in each case one CH₂ group may be replaced by O, or substituted by H, F, Cl, OH, CF₃, NO₂, CN, COO-(C₁-C₄)-alkyl, CONH₂, CONH(C₁-C₄)-alkyl, OCF₃;

and the pharmaceutically acceptable salts thereof.

Preferred compounds of the formula I are those in which the meanings are

R₁, R₂ OH, F or H or R₁ and R₂ = F, where one of the radicals R₁, R₂ must be F;

R₃ OH;

A O or NH;

X S or optionally R₆-substituted N, where Y must be CH when X is S;

Y CH or N;

m a number 1 or 2;

R₄, R₅ hydrogen, F, Cl, Br, I, OH, CF₃, NO₂, CN, COOH, CO(C₁-C₆)-alkyl, COO(C₁-C₆)-alkyl, CONH₂, CONH(C₁-C₆)-alkyl, CON[(C₁-C₆)-alkyl]₂, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₁-C₆)-alkoxy, HO(C₁-C₆)-alkyl, (C₁-C₆)-alkoxy-(C₁-C₆)-alkyl, phenyl, benzyl, SO-(C₁-C₆)-alkyl, it

being possible for one, more than one or all hydrogen(s) in the alkyl radicals to be replaced by fluorine; or when X is S together with the C atoms carrying them phenyl;

- 5 R^6 H, (C₁-C₆)-alkyl, (C₁-C₆)-alkenyl, (C₃-C₅)-cycloalkyl, or phenyl that may optionally be substituted by halogen or (C₁-C₄)-alkyl;
- 10 B (C₀-C₁₅)-alkanediyl, where one or more C atom(s) in the alkanediyl radical may be replaced independently of one another by -O-, -(C=O)-, -CH=CH-, -C≡C-, -S-, -CH(OH)-, -CHF-, -CF₂-, -(S=O)-, -(SO₂)-, -N((C₁-C₆)-alkyl)-, -N((C₁-C₆)-alkyl-phenyl)- or -NH-;
- 15 n a number 2 or 3;
- 20 Cyc1 a 3 to 7 membered saturated, partially saturated or unsaturated ring, where 1 C atom may be replaced by O, N or S;
- 25 R7, R8, R9 hydrogen, F, Cl, Br, I, OH, CF₃, NO₂, CN, COOH, COO(C₁-C₆)-alkyl, CO(C₁-C₄)-alkyl, CONH₂, CONH(C₁-C₆)-alkyl, CON[(C₁-C₆)-alkyl]₂, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₁-C₈)-alkoxy, (C₁-C₆)-alkyl-OH, (C₁-C₆)-alkoxy-(C₁-C₆)-alkyl, SO-(C₁-C₆)-alkyl, it being possible for one, more than one or all hydrogen(s) in the alkyl radicals to be replaced by fluorine;
- 30 R8 and R9 together with the C atoms carrying them a 5 to 7 membered, saturated, partially or completely unsaturated ring Cyc2, where 1 or 2 C atom(s) in the ring may also be replaced by N, O or S, and Cyc2 may optionally be substituted by (C₁-C₆)-alkyl, (C₂-C₅)-alkenyl, (C₂-C₅)-alkynyl, where in each case one CH₂ group may be replaced by O, or substituted by H, F, Cl, OH, CF₃, NO₂, CN, COO(C₁-C₄)-alkyl, CONH₂, CONH(C₁-C₄)-alkyl, OCF₃.
- 35

Further preferred compounds of the formula I are those in which the sugar residues are beta(β)-linked and the stereochemistry in the 2- and 5-position

5	R1, R2	are OH, F or H or R1 and R2 = F, where one of the radicals R1, R2 must be F;
	R3	is OH;
10	A	is O;
	X	S or optionally R6-substituted N, where Y must be CH when X is S;
15	Y	CH or N;
	m	a number 1;
20	R4, R5	are hydrogen, OH, (C1-C5)-alkyl, (C1-C4)-alkoxy, HO-(C1-C4)-alkyl, (C1-C4)-alkoxy-(C1-C4)-alkyl, F, Cl, CF3, OCF3, OCH2CF3 (C1-C4)-alkyl-CF2-, phenyl, benzyl, (C2-C4)-alkenyl, (C2-C4)-alkynyl, COO(C1-C4)-alkyl; or when X is S together with the C atoms carrying them phenyl;
25	R ⁶	H, (C1-C6)-alkyl, (C1-C6)-alkenyl, (C3-C6)-cycloalkyl, or phenyl that may optionally be substituted by halogen or (C1-C4)-alkyl;
	B	is (C1-C4)-alkanediyl, where one CH2 group may also be replaced by -(C=O)-, -CH(OH)-, -CO-NH-, -CHF-, -CF2-, -O-;
30	n	is a number 2 or 3;
	Cyc1	is unsaturated 5- or 6-membered ring, where 1 C atom may be replaced by O, N or S;
35	R7, R8, R9	are hydrogen, (C1-C4)-alkyl, (C1-C8)-alkoxy, OCF3, OCH2CF3, OH, (C1-C4)-alkyl-OH, (C1-C4)-alkoxy-(C1-C4)-alkyl, or

R8 and R9 together are $-\text{CH}=\text{CH}-\text{O}-$, $-\text{CH}=\text{CH}-\text{S}-$, $-\text{O}-(\text{CH}_2)_p-\text{O}-$, with $p = 1$ or 2 , and

R7 is hydrogen.

5

Very particularly preferred compounds of the formula I are those in which

R1 is F and R2 is H or

R1 is H and R2 is F;

10

R3 is OH;

A is O;

15 X S or optionally R6-substituted N, where Y must be CH when X is S;

Y CH or N;

20 m a number 1;

R4, R5 are hydrogen, OH, CF_3 , (C_1-C_3) -alkyl, or when X is S together with the C atoms carrying them phenyl;

25 R6 H, (C_1-C_4) -alkyl or phenyl;

B is $-\text{CH}_2-$, $-\text{C}_2\text{H}_4-$, $-\text{C}_3\text{H}_6-$, $-\text{CO}-\text{NH}-\text{CH}_2-$ or $-\text{CO}-\text{CH}_2-\text{CH}_2-$;

n is a number 2 or 3;

30

Cyc1 is unsaturated 6-membered ring, where 1 C atom may be replaced by N;

R7, R8, R9 are hydrogen, (C_1-C_4) -alkyl, (C_1-C_7) -alkoxy, OCF_3 or

35

R8 and R9 together are $-\text{CH}=\text{CH}-\text{O}-$, $-\text{O}-(\text{CH}_2)_p-\text{O}-$, with $p = 1$ or 2 , and

R7 is hydrogen.

Further very particularly preferred compounds of the formula I are those in which

- 5 R1 is F and R2 is H or
 R1 is H and R2 is F;
- R3 is OH;
- 10 A is O;
- X S or optionally R6-substituted N, where Y must be CH when
 X is S;
- Y CH or N;
- 15 m a number 1;
- R4 is hydrogen, methyl or CF₃,
- 20 R5 hydrogen or
- R4 and R5 when X is S together with the C atoms carrying them phenyl;
- R6 H, (C₁-C₄)-alkyl or phenyl;
- 25 B is -CH₂-, -CO-CH₂-CH₂- or -CO-NH-CH₂-;
- n is a number 3;
- 30 Cyc1 is unsaturated 6-membered ring;
- R7, R8, R9 are hydrogen or methoxy.

35 Additional very particularly preferred compounds which may be mentioned are those in which X is S and those in which R1 is F and R2 is H.

The invention relates to compounds of the formula I in the form of their racemates, racemic mixtures and pure enantiomers and to their diastereomers and mixtures thereof.

The alkyl radicals in the substituents R4, R5, R6, R7, R8 and R9 may be either straight-chain or branched. Halogen preferably means F or Cl.

- 5 Pharmaceutically acceptable salts are, because their solubility in water is greater than that of the initial or basic compounds, particularly suitable for medical applications. These salts must have a pharmaceutically acceptable anion or cation. Suitable pharmaceutically acceptable acid addition salts of the compounds of the invention are salts of inorganic acids such as
- 10 hydrochloric acid, hydrobromic, phosphoric, metaphosphoric, nitric and sulfuric acid, and of organic acids such as, for example, acetic acid, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isethionic, lactic, lactobionic, maleic, malic, methanesulfonic, succinic, p-toluenesulfonic and tartaric acid. Suitable pharmaceutically acceptable
- 15 basic salts are ammonium salts, alkali metal salts (such as sodium and potassium salts), alkaline earth metal salts (such as magnesium and calcium salts), trometamol (2-amino-2-hydroxymethyl-1,3-propanediol), diethanolamine, lysine or ethylenediamine.
- 20 Salts with a pharmaceutically unacceptable anion such as, for example, trifluoroacetate likewise belong within the framework of the invention as useful intermediates for the preparation or purification of pharmaceutically acceptable salts and/or for use in nontherapeutic, for example in vitro, applications.
- 25 The term "physiologically functional derivative" used herein refers to any physiologically tolerated derivative of a compound of the formula I of the invention, for example an ester, which on administration to a mammal such as, for example, a human is able to form (directly or indirectly) a compound
- 30 of the formula I or an active metabolite thereof.

Physiologically functional derivatives include prodrugs of the compounds of the invention, as described, for example, in H. Okada et al., Chem. Pharm. Bull. 1994, 42, 57-61. Such prodrugs can be metabolized in vivo to a

- 35 compound of the invention. These prodrugs may themselves be active or not. Carbonates at the 6 position of the sugar (see WO 0280936 and WO 0244192) are preferred, particularly preferably methyl carbonate and ethyl carbonate.

The compounds of the invention may also exist in various polymorphous forms, for example as amorphous and crystalline polymorphous forms. All polymorphous forms of the compounds of the invention belong within the framework of the invention and are a further aspect of the invention.

5

All references to "compound(s) of formula I" hereinafter refer to compound(s) of the formula I as described above, and their salts, solvates and physiologically functional derivatives as described herein.

- 10 The compound(s) of formula (I) may also be administered in combination with other active ingredients.

The amount of a compound of formula I necessary to achieve the desired biological effect depends on a number of factors, for example the specific
15 compound chosen, the intended use, the mode of administration and the clinical condition of the patient. The daily dose is generally in the range from 0.3 mg to 100 mg (typically from 3 mg and 50 mg) per day and per kilogram of bodyweight, for example 3-10 mg/kg/day. An intravenous dose may be, for example, in the range from 0.3 mg to 1.0 mg/kg, which can
20 suitably be administered as infusion of 10 ng to 100 ng per kilogram and per minute. Suitable infusion solutions for these purposes may contain, for example, from 0.1 ng to 10 mg, typically from 1 ng to 10 mg, per milliliter. Single doses may contain, for example, from 1 mg to 10 g of the active ingredient. Thus, ampoules for injections may contain, for example, from
25 1 mg to 100 mg, and single-dose formulations which can be administered orally, such as, for example, tablets or capsules, may contain, for example, from 1.0 to 1000 mg, typically from 10 to 600 mg. For the therapy of the abovementioned conditions, the compounds of formula I may be used as the compound itself, but they are preferably in the form of a pharmaceutical
30 composition with an acceptable carrier. The carrier must, of course, be acceptable in the sense that it is compatible with the other ingredients of the composition and is not harmful for the patient's health. The carrier may be a solid or a liquid or both and is preferably formulated with the compound as a single dose, for example as a tablet, which may contain
35 from 0.05% to 95% by weight of the active ingredient. Other pharmaceutically active substances may likewise be present, including other compounds of formula I. The pharmaceutical compositions of the invention can be produced by one of the known pharmaceutical methods, which essentially consist of mixing the ingredients with pharmacologically

acceptable carriers and/or excipients.

Pharmaceutical compositions of the invention are those suitable for oral, rectal, topical, peroral (for example sublingual) and parenteral (for example
5 subcutaneous, intramuscular, intradermal or intravenous) administration, although the most suitable mode of administration depends in each individual case on the nature and severity of the condition to be treated and on the nature of the compound of formula I used in each case. Coated formulations and coated slow-release formulations also belong within the
10 framework of the invention. Preference is given to acid- and gastric juice-resistant formulations. Suitable coatings resistant to gastric juice comprise cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl-methylcellulose phthalate and anionic polymers of methacrylic acid and methyl methacrylate.

15 Suitable pharmaceutical compounds for oral administration may be in the form of separate units such as, for example, capsules, cachets, suckable tablets or tablets, each of which contain a defined amount of the compound of formula I; as powders or granules; as solution or suspension in an
20 aqueous or nonaqueous liquid; or as an oil-in-water or water-in-oil emulsion. These compositions may, as already mentioned, be prepared by any suitable pharmaceutical method which includes a step in which the active ingredient and the carrier (which may consist of one or more additional ingredients) are brought into contact. The compositions are
25 generally produced by uniform and homogeneous mixing of the active ingredient with a liquid and/or finely divided solid carrier, after which the product is shaped if necessary. Thus, for example, a tablet can be produced by compressing or molding a powder or granules of the compound, where appropriate with one or more additional ingredients.
30 Compressed tablets can be produced by tableting the compound in free-flowing form such as, for example, a powder or granules, where appropriate mixed with a binder, glidant, inert diluent and/or one (or more) surface-active/dispersing agent(s) in a suitable machine. Molded tablets can be produced by molding the compound, which is in powder form and is
35 moistened with an inert liquid diluent, in a suitable machine.

Pharmaceutical compositions which are suitable for peroral (sublingual) administration comprise suckable tablets which contain a compound of formula I with a flavoring, normally sucrose and gum arabic or tragacanth,

and pastilles which comprise the compound in an inert base such as gelatin and glycerol or sucrose and gum arabic.

5 Pharmaceutical compositions suitable for parenteral administration comprise preferably sterile aqueous preparations of a compound of formula I, which are preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also take place by subcutaneous, intramuscular or intradermal injection. These preparations can preferably be produced by
10 mixing the compound with water and making the resulting solution sterile and isotonic with blood. Injectable compositions of the invention generally contain from 0.1 to 5% by weight of the active compound.

15 Pharmaceutical compositions suitable for rectal administration are preferably in the form of single-dose suppositories. These can be produced by mixing a compound of the formula I with one or more conventional solid carriers, for example cocoa butter, and shaping the resulting mixture.

20 Pharmaceutical compositions suitable for topical use on the skin are preferably in the form of ointment, cream, lotion, paste, spray, aerosol or oil. Carriers which can be used are petrolatum, lanolin, polyethylene glycols, alcohols and combinations of two or more of these substances. The active ingredient is generally present in a concentration of from 0.1 to 15% by weight of the composition, for example from 0.5 to 2%.

25 Transdermal administration is also possible. Pharmaceutical compositions suitable for transdermal uses can be in the form of single plasters which are suitable for long-term close contact with the patient's epidermis. Such plasters suitably contain the active ingredient in an aqueous solution which
30 is buffered where appropriate, dissolved and/or dispersed in an adhesive or dispersed in a polymer. A suitable active ingredient concentration is about 1% to 35%, preferably about 3% to 15%. A particular possibility is for the active ingredient to be released by electrotransport or iontophoresis as described, for example, in *Pharmaceutical Research*, 2(6): 318 (1986).

35 Further active ingredients suitable for combination products are:
all antidiabetics mentioned in the Rote Liste 2001, chapter 12. They may be combined with the compounds of the formula I of the invention in particular for synergistic improvement of the effect. Administration of the active

ingredient combination may take place either by separate administration of the active ingredients to the patient or in the form of combination products in which a plurality of active ingredients are present in one pharmaceutical preparation. Most of the active ingredients listed below are disclosed in the
5 USP Dictionary of USAN and International Drug Names, US Pharmacopeia, Rockville 2001.

Antidiabetics include insulin and insulin derivatives such as, for example, Lantus® (see www.lantus.com) or HMR 1964, fast-acting insulins (see
10 US 6,221,633), GLP-1 derivatives such as, for example, those disclosed in WO 98/08871 of Novo Nordisk A/S, and orally effective hypoglycemic active ingredients.

The orally effective hypoglycemic active ingredients include, preferably,
15 sulfonylureas, biguanidines, meglitinides, oxadiazolidinediones, thiazolidinediones, glucosidase inhibitors, glucagon antagonists, GLP-1 agonists, potassium channel openers such as, for example, those disclosed in WO 97/26265 and WO 99/03861 of Novo Nordisk A/S, insulin sensitizers, inhibitors of liver enzymes involved in the stimulation of
20 gluconeogenesis and/or glycogenolysis, modulators of glucose uptake, compounds which alter lipid metabolism, such as antihyperlipidemic active ingredients and antilipidemic active ingredients, compounds which reduce food intake, PPAR and PXR agonists and active ingredients which act on the ATP-dependent potassium channel of the beta cells.

25 In one embodiment of the invention, the compounds of the formula I are administered in combination with an HMGCoA reductase inhibitor such as simvastatin, fluvastatin, pravastatin, lovastatin, atorvastatin, cerivastatin, rosuvastatin.

30 In one embodiment of the invention, the compounds of the formula I are administered in combination with a cholesterol absorption inhibitor such as, for example, ezetimibe, tiqueside, pamaqueside.

35 In one embodiment of the invention, the compounds of the formula I are administered in combination with a PPAR gamma agonist, such as, for example, rosiglitazone, pioglitazone, JTT-501, GI 262570.

In one embodiment of the invention, the compounds of the formula I are

administered in combination with a PPAR alpha agonist, such as, for example, GW 9578, GW 7647.

5 In one embodiment of the invention, the compounds of the formula I are administered in combination with a mixed PPAR alpha/gamma agonist, such as, for example, GW 1536, AVE 8042, AVE 8134, AVE 0847, or as described in PCT/US 11833, PCT/US 11490, DE10142734.4.

10 In one embodiment of the invention, the compounds of the formula I are administered in combination with a fibrate such as, for example, fenofibrate, clofibrate, bezafibrate.

15 In one embodiment of the invention, the compounds of the formula I are administered in combination with an MTP inhibitor such as, for example, implitapide, BMS-201038, R-103757.

20 In one embodiment of the invention, the compounds of the formula I are administered in combination with bile acid absorption inhibitor (see, for example, US 6,245,744 or US 6,221,897), such as, for example, HMR 1741.

25 In one embodiment of the invention, the compounds of the formula I are administered in combination with a CETP inhibitor, such as, for example, JTT-705.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a polymeric bile acid adsorbent such as, for example, cholestyramine, colesevelam.

30 In one embodiment of the invention, the compounds of the formula I are administered in combination with an LDL receptor inducer (see US 6,342,512), such as, for example, HMR1171, HMR1586.

35 In one embodiment of the invention, the compounds of the formula I are administered in combination with an ACAT inhibitor, such as, for example, avasimibe.

In one embodiment of the invention, the compounds of the formula I are administered in combination with an antioxidant, such as, for example,

OPC-14117.

5 In one embodiment of the invention, the compounds of the formula I are administered in combination with a lipoprotein lipase inhibitor, such as, for example, NO-1886.

10 In one embodiment of the invention, the compounds of the formula I are administered in combination with an ATP-citrate lyase inhibitor, such as, for example, SB-204990.

15 In one embodiment of the invention, the compounds of the formula I are administered in combination with a squalene synthetase inhibitor, such as, for example, BMS-188494.

20 In one embodiment of the invention, the compounds of the formula I are administered in combination with a lipoprotein(a) antagonist, such as, for example, CI-1027 or nicotinic acid.

25 In one embodiment of the invention, the compounds of the formula I are administered in combination with a lipase inhibitor, such as, for example, orlistat.

30 In one embodiment of the invention, the compounds of the formula I are administered in combination with insulin.

35 In one embodiment, the compounds of the formula I are administered in combination with a sulfonylurea such as, for example, tolbutamide, glibenclamide, glipizide or glimepiride.

40 In one embodiment, the compounds of the formula I are administered in combination with a biguanide, such as, for example, metformin.

45 In one further embodiment, the compounds of the formula I are administered in combination with a meglitinide, such as, for example, repaglinide.

50 In one embodiment, the compounds of the formula I are administered in combination with a thiazolidinedione, such as, for example, troglitazone, ciglitazone, pioglitazone, rosiglitazone or the compounds disclosed in

WO 97/41097 of Dr. Reddy's Research Foundation, in particular 5-[[4-[(3,4-dihydro-3-methyl-4-oxo-2-quinazolinylmethoxy)phenyl]methyl]-2,4-thiazolidinedione.

- 5 In one embodiment, the compounds of the formula I are administered in combination with an α -glucosidase inhibitor, such as, for example, miglitol or acarbose.

- 10 In one embodiment, the compounds of the formula I are administered in combination with an active ingredient which acts on the ATP-dependent potassium channel of the beta cells, such as, for example, tolbutamide, glibenclamide, glipizide, glimepiride or repaglinide.

- 15 In one embodiment, the compounds of the formula I are administered in combination with more than one of the aforementioned compounds, e.g. in combination with a sulfonylurea and metformin, with a sulfonylurea and acarbose, repaglinide and metformin, insulin and a sulfonylurea, insulin and metformin, insulin and troglitazone, insulin and lovastatin, etc.

- 20 In a further embodiment, the compounds of the formula I are administered in combination with CART modulators (see "Cocaine-amphetamine-regulated transcript influences energy metabolism, anxiety and gastric emptying in mice" Asakawa, A, et al., M.: Hormone and Metabolic Research (2001), 33(9), 554-558), NPY antagonists, e.g. naphthalene-25 1-sulfonic acid {4-[(4-aminoquinazolin-2-ylamino)methyl]-cyclohexylmethyl}amide; hydrochloride (CGP 71683A)), MC4 agonists (e.g. 1-amino-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid [2-(3a-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydropyrazolo[4,3-c]pyridin-5-yl)-1-(4-chlorophenyl)-2-oxoethyl]-amide; (WO 01/91752)), orexin antagonists (e.g. 30 1-(2-methylbenzoxazol-6-yl)-3-[1,5]naphthyridin-4-ylurea; hydrochloride (SB-334867-A)), H3 agonists (3-cyclohexyl-1-(4,4-dimethyl-1,4,6,7-tetrahydroimidazo[4,5-c]pyridin-5-yl)propan-1-one oxalic acid salt (WO 00/63208)), TNF agonists, CRF antagonists (e.g. [2-methyl-9-(2,4,6-trimethylphenyl)-9H-1,3,9-triazafuoren-4-yl]dipropylamine (WO 00/66585)), 35 CRF BP antagonists (e.g. urocortin), urocortin agonists, β 3 agonists (e.g. 1-(4-chloro-3-methanesulfonylmethylphenyl)-2-[2-(2,3-dimethyl-1H-indol-6-yloxy)ethylamino]-ethanol hydrochloride (WO 01/83451)), MSH (melanocyte-stimulating hormone) agonists, CCK-A agonists (e.g. {2-[4-(4-chloro-2,5-dimethoxyphenyl)-5-(2-cyclohexylethyl)thiazol-2-yl-

carbamoyl]-5,7-dimethylindol-1-yl}acetic acid trifluoroacetic acid salt (WO 99/15525)), serotonin reuptake inhibitors (e.g. dexfenfluramine), mixed serotonergic and noradrenergic compounds (e.g. WO 00/71549), 5HT agonists e.g. 1-(3-ethylbenzofuran-7-yl)piperazine oxalic acid salt (WO 01/09111), bombesin agonists, galanin antagonists, growth hormone (e.g. human growth hormone), growth hormone-releasing compounds (6-benzyloxy-1-(2-diisopropylaminoethylcarbamoyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (WO 01/85695)), TRH agonists (see, for example, EP 0 462 884) uncoupling protein 2 or 3 modulators, leptin agonists (see, for example, Lee, Daniel W.; Leinung, Matthew C.; Rozhavskaya-Arena, Marina; Grasso, Patricia. Leptin agonists as a potential approach to the treatment of obesity. *Drugs of the Future* (2001), 26(9), 873-881), DA agonists (bromocriptine, Doprexin), lipase/amylase inhibitors (e.g. WO 00/40569), PPAR modulators (e.g. WO 00/78312), RXR modulators or TR- β agonists.

In one embodiment of the invention, the other active ingredient is leptin; see, for example, "Perspectives in the therapeutic use of leptin", Salvador, Javier; Gomez-Ambrosi, Javier; Fruhbeck, Gema, *Expert Opinion on Pharmacotherapy* (2001), 2(10), 1615-1622.

In one embodiment, the other active ingredient is dexamphetamine or amphetamine.

In one embodiment, the other active ingredient is fenfluramine or dexfenfluramine.

In another embodiment, the other active ingredient is sibutramine.

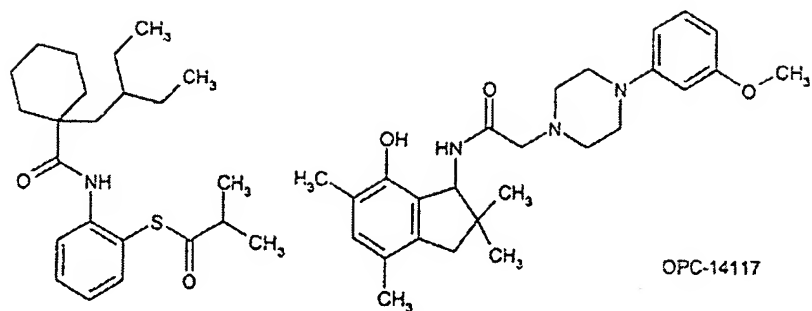
In one embodiment, the other active ingredient is orlistat.

In one embodiment, the other active ingredient is mazindol or phentermine.

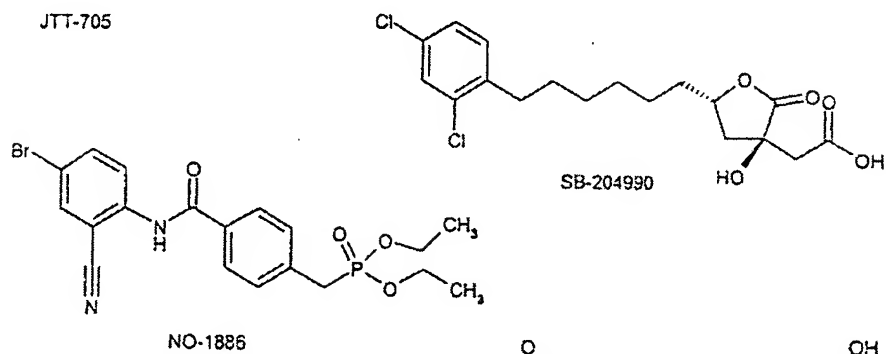
In one embodiment, the compounds of the formula I are administered in combination with bulking agents, preferably insoluble bulking agents (see, for example, carob/Caromax[®] (Zunft H J; et al., Carob pulp preparation for treatment of hypercholesterolemia, *ADVANCES IN THERAPY* (2001 Sep-Oct), 18(5), 230-6.) Caromax is a carob-containing product from Nutrinova, Nutrition Specialties & Food Ingredients GmbH, Industriepark

Höchst, 65926 Frankfurt/Main)). Combination with Caromax[®] is possible in one preparation or by separate administration of compounds of the formula I and Caromax[®]. Caromax[®] can in this connection also be administered in the form of food products such as, for example, in bakery products or muesli bars.

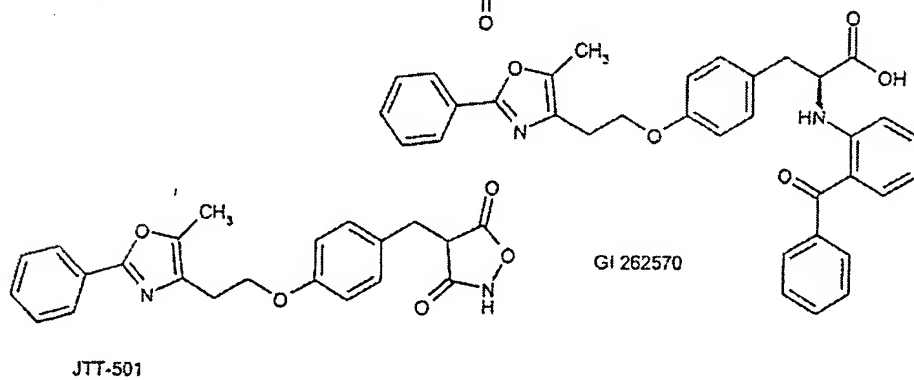
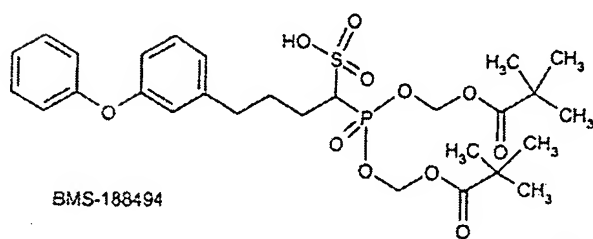
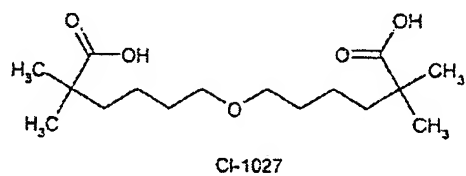
It will be appreciated that every suitable combination of the compounds of the invention with one or more of the aforementioned compounds and optionally one or more other pharmacologically active substances is regarded as falling within the protection conferred by the present invention.



JTT-705



SB-204990

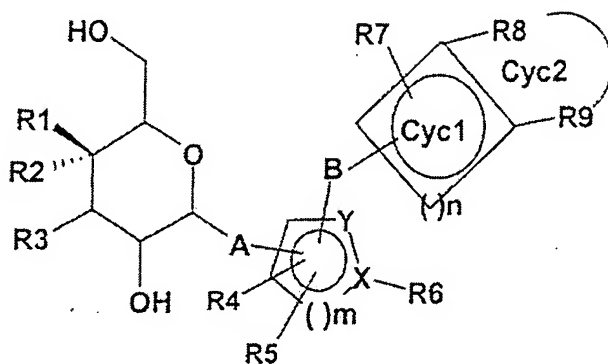


GI 262570

The examples detailed below serve to illustrate the invention without, however, restricting it.

Table 1: Compounds of the formula I

5



Ex.	R1	R2	R3	R4, R5	R6	R7	R8, R9
1	H	F	OH	H, H	-	4-O-CH ₃	H, H
2	H	F	OH	-CH=CH-CH=CH-	-	4-O-CH ₃	H, H
3	F	H	OH	H, H	-	4-O-CH ₃	H, H
4	H	OH	F	H, H	-	4-O-CH ₃	H, H
5	H	F	OH	CF ₃ , H	H	4-O-CH ₃	H, H
6	F	H	OH	CF ₄ , H	H	4-O-CH ₃	H, H

Ex.	A	B	Cyc1	X	Y	M	N	MS*
1	O	CH ₂	Ph	S	CH	1	3	ok
2	O	CH ₂	Ph	S	CH	1	3	ok
3	O	CH ₂	Ph	S	CH	1	3	ok
4	O	CH ₂	Ph	S	CH	1	3	ok
5	O	CH ₂	Ph	N	N	1	3	ok
6	O	CH ₂	Ph	N	N	1	3	ok

- 10 * The indication "MS is ok" means that a mass spectrum or HPLC/MS was recorded and the molecular peak (molecular mass + H⁺) was detected therein

- 15 The compounds of the formula I are distinguished by beneficial effects on glucose metabolism; in particular, they lower the blood glucose level and are suitable for the treatment of type 1 and type 2 diabetes. The

compounds can therefore be employed alone or in combination with other blood glucose-lowering active ingredients (antidiabetics).

The compounds of the formula I are further suitable for the prevention and treatment of late damage from diabetes, such as, for example, nephropathy, retinopathy, neuropathy and syndrome X, obesity, myocardial infarct, myocardial infarction, peripheral arterial occlusive diseases, thromboses, arteriosclerosis, inflammations, immune diseases, autoimmune diseases such as, for example, AIDS, asthma, osteoporosis, cancer, psoriasis, Alzheimer's, schizophrenia and infectious diseases, with preference for the treatment of type 1 and type 2 diabetes and the prevention and treatment of late damage from diabetes, syndrome X and obesity.

The activity of the compounds was tested as follows:

Preparation of brush border membrane vesicles from the small intestine of rabbits, rats and pigs

Preparation of brush border membrane vesicles from the intestinal cells of the small intestine was carried out by the so-called Mg^{2+} precipitation method. The mucosa of the small intestine was scraped off and suspended in 60 ml of ice-cold Tris/HCl buffer (pH 7.1)/300 mM mannitol, 5 mM EGTA. Dilution to 300 ml with ice-cold distilled water was followed by homogenization with an Ultraturrax (18 shaft, IKA Werk Staufen, FRG) at 75% of the max. power for 2×1 minute, while cooling in ice. After addition of 3 ml of 1M $MgCl_2$ solution (final concentration 10 mM), the mixture is left to stand at $0^\circ C$ for exactly 15 minutes. Addition of Mg^{2+} causes the cell membranes to aggregate and precipitate with the exception of the brush border membranes. After centrifugation at $3\,000 \times g$ (5 000 rpm, SS-34 rotor) for 15 minutes, the precipitate is discarded and the supernatant, which contains the brush border membranes, is centrifuged at $26\,700 \times g$ (15 000 rpm, SS-34 rotor) for 30 minutes. The supernatant is discarded, and the precipitate is rehomogenized in 60 ml of 12 mM Tris/HCl buffer (pH 7.1)/60 mM mannitol, 5 mM EGTA using a Potter Elvehjem homogenizer (Braun, Melsungen, 900 rpm, 10 strokes). Addition of 0.1 ml of 1M $MgCl_2$ solution and incubation at $0^\circ C$ for 15 minutes is followed by centrifugation again at $3\,000 \times g$ for 15 minutes. The supernatant is then centrifuged again at $46\,000 \times g$ (20 000 rpm, SS-34 rotor) for 30 minutes. The precipitate is taken up in 30 ml of 20 mM Tris/Hepes buffer

(pH 7.4)/280 mM mannitol and homogeneously resuspended by 20 strokes in a Potter Elvehjem homogenizer at 1 000 rpm. After centrifugation at $48\,000 \times g$ (20 000 rpm, SS-34 rotor) for 30 minutes, the precipitate was taken up in 0.5 to 2 ml of Tris/Hepes buffer (pH 7.4)/280 mM mannitol (final concentration 20 mg/ml) and resuspended using a tuberculin syringe with a 27 gauge needle.

The vesicles were either used directly after preparation for labeling or transport studies or were stored at -196°C in 4 mg portions in liquid nitrogen.

To prepare brush border membrane vesicles from rat small intestine, 6 to 10 male Wistar rats (bred at Kastengrund, Aventis Pharma) were sacrificed by cervical dislocation, and the small intestines were removed and rinsed with cold isotonic saline. The intestines were cut up and the mucosa was scraped off. The processing to isolate brush border membranes took place as described above. To remove cytoskeletal fractions, the brush border membrane vesicles from rat small intestine were treated with KSCN as chaotropic ion.

To prepare brush border membranes from rabbit small intestine, rabbits were sacrificed by intravenous injection of 0.5 ml of an aqueous solution of 2.5 mg of tetracaine HCl, 100 mg of m-butramide and 25 mg of mebezonium iodide. The small intestines were removed, rinsed with ice-cold physiological saline and stored frozen in plastic bags under nitrogen at -80°C and 4 to 12 weeks. For preparation of the membrane vesicles, the frozen intestines were thawed at 30°C in a water bath and then the mucosa was scraped off. Processing to give membrane vesicles took place as described above.

To prepare brush border membrane vesicles from pig intestine, jejunum segments from a freshly slaughtered pig were rinsed with ice-cold isotonic saline and frozen in plastic bags under nitrogen at -80°C . Preparation of the membrane vesicles took place as described above.

Preparation of brush border membrane vesicles from the renal cortex of the rat kidney

Brush border membrane vesicles were prepared from the cortex of the rat kidney by the method of Biber et al. The kidneys from 6 to 8 rats (200 to 250 g) were removed and the cortex was cut off each kidney as a layer

about 1 mm thick. The kidneys were taken up in 30 ml of ice-cold 12 mM Tris/HCl buffer (pH 7.4)/300 mM mannitol and homogenized with an Ultraturrax shaft (level 180 V) for 4 × 30 seconds while cooling in ice. Addition of 42 ml of ice-cold distilled water was followed by addition of
 5 850 µl of a 1M MgCl₂ solution. Incubation at 0°C for 15 minutes was followed by centrifugation at 4 500 rpm (Sorvall SS-34 rotor) for 15 minutes. The precipitate was discarded, and the supernatant was centrifuged at 16 000 rpm for 30 minutes. Resuspension of the precipitate in 60 ml of 6 mM Tris/HCl buffer (pH 7.4)/150 mM mannitol/2.5 mM EGTA
 10 by 10 strokes in a Potter-Elvehjem homogenizer (900 rpm) and addition of 720 µl of 1 mM MgCl₂ solution was followed by incubation at 0°C for 15 minutes. The supernatant resulting after centrifugation at 4 500 rpm (SS-34 rotor) for 15 minutes was centrifuged at 16 000 rpm for 30 minutes. The supernatant was homogenized by 10 strokes in 60 ml of 20 mM
 15 Tris/Hepes buffer (pH 7.4)/280 mM mannitol, and the resulting suspension was then centrifuged at 20 000 rpm for 30 minutes. The precipitate was resuspended in 20 mM Tris/HCl buffer (pH 7.4)/280 mM mannitol using a tuberculin syringe with a 27 gauge needle and was adjusted to a protein concentration of 20 mg/ml.

20

Measurement of the glucose uptake by brush border membrane vesicles

The uptake of [¹⁴C]-labeled glucose into brush border membrane vesicles was measured by the membrane filtration method. 10 µl of the brush
 25 border membrane vesicle suspension in 10 mM Tris/Hepes buffer (pH 7.4)/300 mM mannitol were added at 20°C to 90 µl of a solution of 10 pM [¹⁴C]D glucose and the appropriate concentrations of the relevant inhibitors (5-200 µM) in 10 mM Tris/Hepes buffer (pH 7.4)/100 mM NaCl/100 mM [lacuna].
 30 After incubation for 15 seconds, the transport process was stopped by adding 1 ml of ice-cold stop solution (10 mM Tris/Hepes buffer (pH 7.4)/150 mM KCl) and the vesicle suspension was immediately filtered with suction through a cellulose nitrate membrane filter (0.45 µm, 25 mm diameter, Schleicher & Schüll) under a vacuum of from 25 to 35 mbar. The
 35 filter was washed with 5 ml of ice-cold stop solution. Each measurement was carried out as duplicate or triplicate determination. To measure the uptake of radiolabeled substrates, the membrane filter was dissolved in 4 ml of an appropriate scintillator (Quickszint 361, Zinsser Analytik GmbH, Frankfurt am Main), and the radioactivity was determined by liquid

scintillation measurement. The measured values were obtained as dpm (decompositions per minute) after calibration of the instrument using standard samples and after correction for any chemiluminescence present.

- 5 The active ingredients are compared for activity on the basis of IC₂₅ data obtained in the transport assay on rabbit small intestine brush border membrane vesicles for selected substances. (The absolute values may be species- and experiment-dependent)

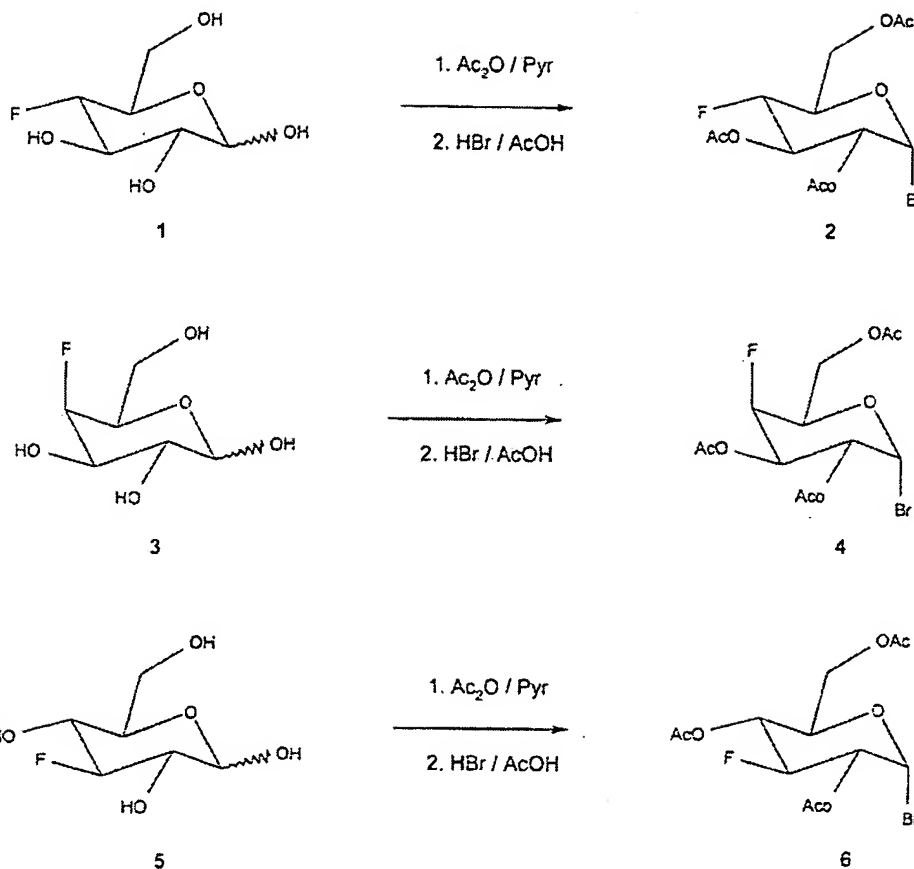
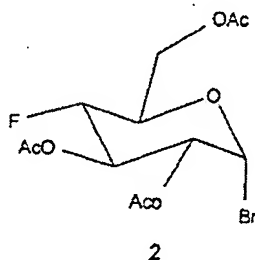
Example No.	IC50 [μ M]
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Phlorizin	16
1	4
2	0.4
3	0.3

10

The preparation of various examples is described in detail below, and the other compounds of the formula I were obtained analogously:

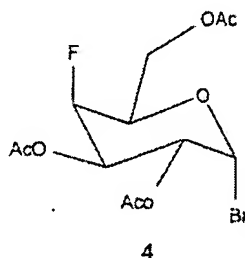
Experimental part:

5 1-Bromo-4-deoxy-4-fluoro-2,3,6-tri-O-acetyl- α -D-glucose 2

5 g (27.5 mmol) of 4-deoxy-4-fluoro-D-glucopyranose 1 (Apollo) are
 10 suspended in 50 ml of pyridine and 50 ml of acetic anhydride. The reaction
 solution is stirred at 45°C for 4 hours. This results in a clear reaction
 solution which is then concentrated. 12 g of crude product are obtained.
 This crude product is dissolved in 160 ml of 33% strength HBr in glacial
 acetic acid and left to stand at room temperature for 2 hours. The reaction

solution is then poured into a mixture of 300 g of ice and 300 ml of ethyl acetate. The organic phase is washed twice more with aqueous NaCl solution, filtered through a little silica gel and concentrated. The residue is separated by chromatography on silica gel (ethyl acetate/heptane = 1/1).
 5 8.19 g (80% over 2 stages) of **2** are obtained as a pale yellow solid.

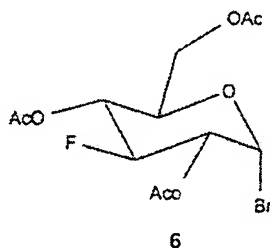
1-Bromo-4-deoxy-4-fluoro-2,3,6-tri-O-acetyl- α -D-galactose **4**



10

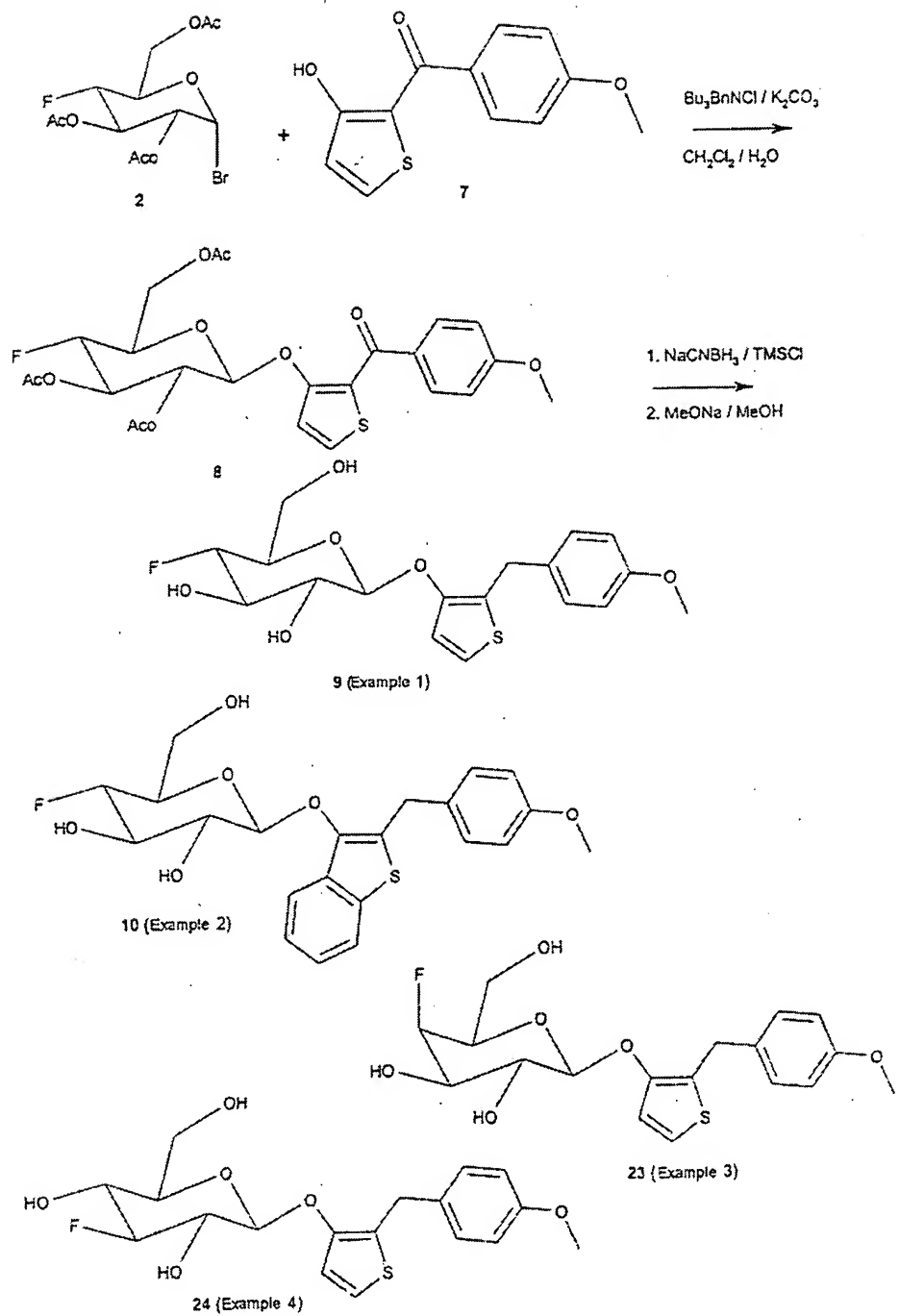
100 mg (0.55 mmol) of **3** are reacted with 3.5 ml of pyridine and 3.5 ml of acetic anhydride in analogy to the preparation of compound **2**. 89 mg (44%) of **4** are obtained as an amorphous solid.

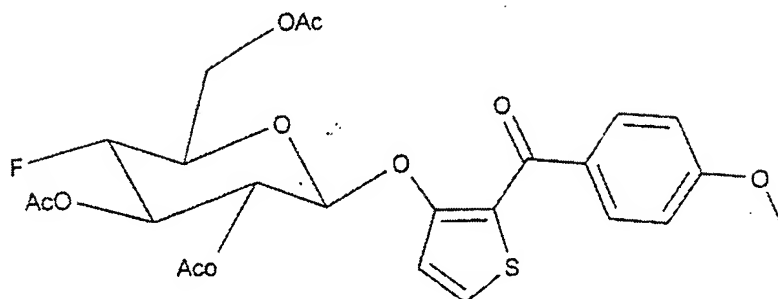
1-Bromo-3-deoxy-3-fluoro-2,3,6-tri-O-acetyl- α -D-glucose **6**



20

335 mg (1.84 mmol) of **5** are reacted with 10 ml of pyridine and 10 ml of acetic anhydride in analogy to the preparation of compound **2**. 628 mg (92%) of **6** are obtained as an amorphous solid.

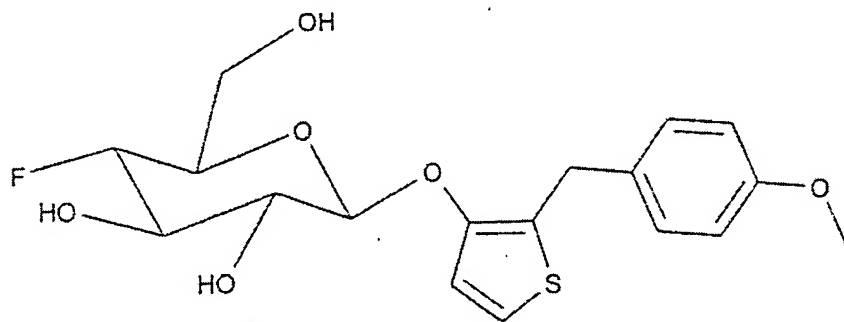


Example 1 (compound 9)

8

5 400 mg (1.7 mmol) of (3-hydroxythiophen-2-yl)(4-methoxyphenyl)-
methanone 7 and 200 mg (0.54 mmol) of bromide 2 are dissolved in 6 ml of
methylene chloride. 160 mg of Bu₃BnNCl (PTC = phase transfer catalyst),
320 mg of K₂CO₃ and 0.4 ml of water are successively added to this
solution, which is then stirred at room temperature for 20 hours. The
10 reaction solution is diluted with 20 ml of ethyl acetate and filtered through
silica gel. The filtrate is concentrated and the residue is separated by
chromatography on silica gel (ethyl acetate/heptane = 1/1). 160 mg (56%)
of 8 are obtained as a colorless solid. C₂₄H₂₅FO₁₀S (524.52) MS(ESI⁺)
525.12 (M + H⁺).

15

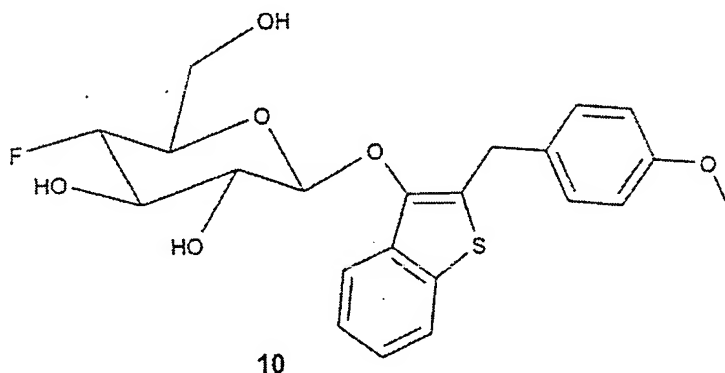


9

150 mg (0.29 mmol) of compound 8 are dissolved in 4 ml of acetonitrile.
This solution is cooled in an ice bath and then 150 mg of NaCNBH₃ and
20 0.2 ml of TMSCl are added. The cooling is then removed and the mixture is
stirred at room temperature for 2 hours. The reaction solution is diluted with
20 ml of ethyl acetate and filtered through silica gel. The filtrate is
concentrated, and 150 mg of crude product are obtained. This crude

product is taken up in 4 ml of methanol, and 1 ml of 1 N NaOMe/MeOH is added. After one hour, the mixture is neutralized with methanolic HCl and concentrated, and the residue is separated by chromatography on silica gel (methylene chloride/methanol/conc. ammonia, 30/5/1). 76 mg (69% over 2 stages) of 9 are obtained as a colorless solid. $C_{18}H_{21}FO_5S$ (384.43) ME(ESI⁺) 403.21 (M + H₂O + H⁺).

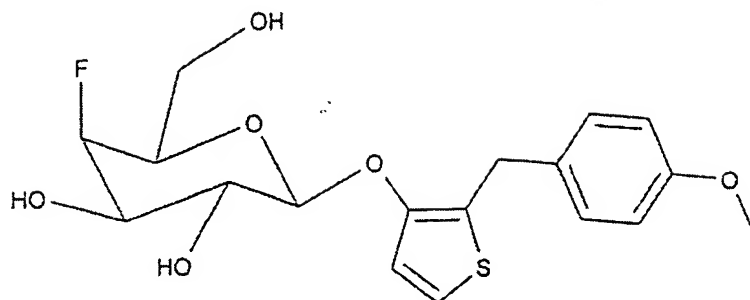
Example 2 (compound 10)



100 mg (0.47 mmol) of (3-hydroxybenzothiophene-2-yl)(4-methoxyphenyl)-methanone and 300 mg (0.80 mmol) of bromide 2 are dissolved in 10 ml of chloroform. 120 mg of Bu₃BnNCl (PTC = phase-transfer catalyst) and 1.5 ml of 1 N aqueous sodium hydroxide solution are successively added to this solution, which is then boiled under reflux for 4 hours. The reaction solution is diluted with 20 ml of ethyl acetate and filtered through silica gel. The filtrate is concentrated and the residue is separated by chromatography on silica gel (ethyl acetate/heptane = 1/1). 135 mg (51%) of pale yellow solid are obtained. This is converted into compound 10 with 100 mg of NaCNBH₃ and 0.2 ml of TMSCl and then with NaOMe/MeOH in analogy to the preparation of compound 9. 46 mg of 10 are obtained. $C_{22}H_{23}FO_6S$ (434.49) MS(ESI⁻) 479.18 (M + CHO₂⁻).

Example 3 (compound 23)

30

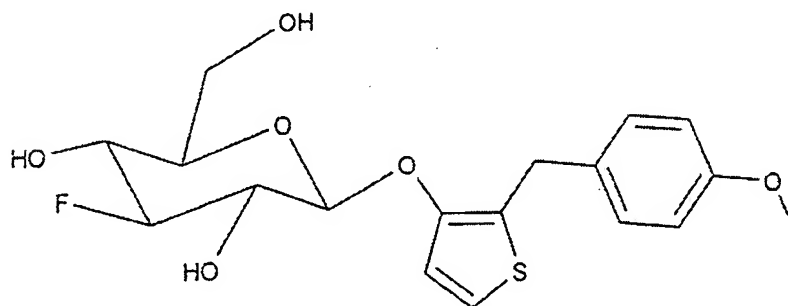


23

178 mg of (3-hydroxythiophen-2-yl)(4-methoxyphenyl)methanone **7** and 90 mg of bromide **4** are reacted in analogy to the synthesis of example 1, and 49 mg of **23** are obtained as a colorless solid. $C_{18}H_{21}FO_6S$ (384.43) MS(ESI⁺) 403.21 (M + H₂O + H⁺).

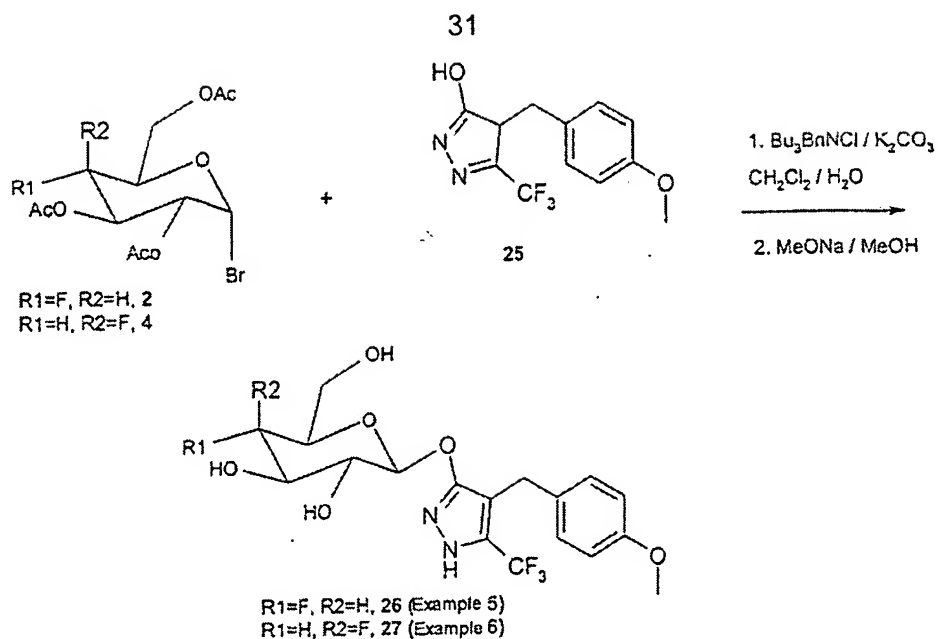
Example 4 (compound **24**)

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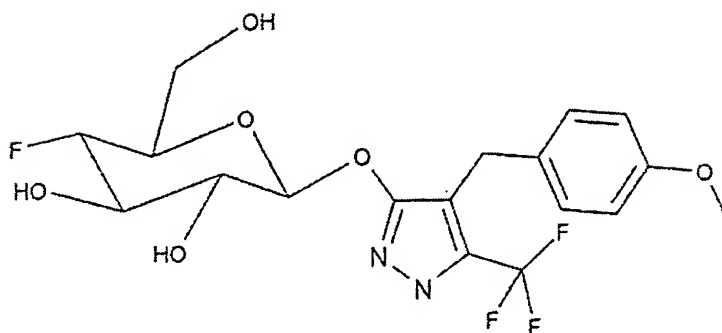
24

200 mg of (3-hydroxythiophen-2-yl)(4-methoxyphenyl)methanone **7** and 100 mg of bromide **6** are reacted in analogy to the synthesis of example 1, and 59 mg of **24** are obtained as a colorless solid.. $C_{18}H_{21}FO_6S$ (384.43) MS(ESI⁺) 403.21 (M + H₂O + H⁺).



Example 5 (compound 25)

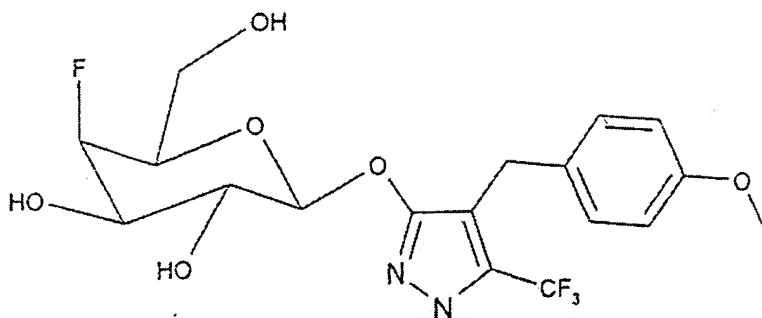
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26

200 mg of 4-(4-methoxybenzyl)-5-methyl-1H-pyrazol-3-ol 25 and 100 mg of
bromide 2 are glycosidated in analogy to the synthesis of example 1 and
then deprotected with NaOMe/MeOH in analogy to example 1, and 49 mg
of 26 are obtained as a colorless solid.. C₁₈H₂₀F₄N₂O₆ (436.36) MS(ESI⁺)
437.21 (M + H⁺).

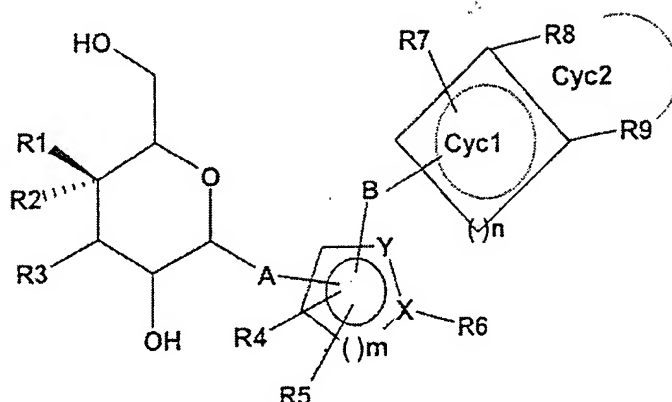
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Example 6 (compound 26)**27**

- 5 200 mg of 4-(4-methoxybenzyl)-5-methyl-1H-pyrazol-3-ol **25** and 100 mg of bromide **4** are glycosidated in analogy to the synthesis of example 1 and then deprotected with NaOMe/MeOH in analogy to example 1, and 89 mg of **27** are obtained as a colorless solid.. C₁₈H₂₀F₄N₂O₆ (436.36) MS(ESI⁺) 437.21 (M + H⁺).

Patent claims

1. A compound of the formula I



in which the meanings are

R1, R2 OH, F or H or R1 and R2 = F;

R3 OH or F, where one of the R1, R2, R3 radicals must be F;

A O, NH, CH₂, S or a bond;

X O, S or optionally R₆-substituted N, where Y must be CH when X is O or S;

Y CH, N, O, S;

m a number 1 or 2;

R4, R5 hydrogen, F, Cl, Br, I, OH, CF₃, NO₂, CN, COOH, CO(C₁-C₆)-alkyl, COO(C₁-C₆)-alkyl, CONH₂, CONH(C₁-C₆)-alkyl, CON[(C₁-C₆)-alkyl]₂, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₁-C₆)-alkoxy, HO(C₁-C₆)-alkyl, (C₁-C₆)-alkoxy-(C₁-C₆)-alkyl, phenyl, benzyl, it being possible for one, more than one or all hydrogen(s) in the alkyl radicals to be replaced by fluorine;

- SO₂-NH₂, SO₂NH(C₁-C₆)-alkyl, SO₂N[(C₁-C₆)-alkyl]₂,
 S-(C₁-C₆)-alkyl, S-(CH₂)_o-phenyl, SO-(C₁-C₆)-alkyl,
 SO-(CH₂)_o-phenyl, SO₂-(C₁-C₆)-alkyl,
 SO₂-(CH₂)_o-phenyl, where o can be 0-6, and the
 phenyl radical may be substituted up to twice by F, Cl,
 Br, OH, CF₃, NO₂, CN, OCF₃, O-(C₁-C₆)-alkyl,
 (C₁-C₆)-alkyl, NH₂;
 NH₂, NH-(C₁-C₆)-alkyl, N[(C₁-C₆)-alkyl]₂, NH(C₁-C₇)-
 acyl, phenyl, O-(CH₂)_o-phenyl, where o can be 0-6,
 where the phenyl ring may be substituted one to 3
 times by F, Cl, Br, I, OH, CF₃, NO₂, CN, OCF₃,
 O-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl, NH₂, NH(C₁-C₆)-alkyl,
 N[(C₁-C₆)-alkyl]₂, SO₂-CH₃, COOH, COO-(C₁-C₆)-
 alkyl, CONH₂;
 when X is S together with the C atoms carrying them
 phenyl;
- R⁶ H, (C₁-C₆)-alkyl, (C₁-C₆)-alkenyl, (C₃-C₆)-cycloalkyl, or
 phenyl that may optionally be substituted by halogen or
 (C₁-C₄)-alkyl;
- B (C₀-C₁₅)-alkanediyl, it being possible for one or more
 C atoms in the alkanediyl radical to be replaced
 independently of one another by -O-, -(C=O)-,
 -CH=CH-, -C≡C-, -S-, -CH(OH)-, -CHF-, -CF₂-,
 -(S=O)-, -(SO₂)-, -N[(C₁-C₆)-alkyl]-, -N[(C₁-C₆)-alkyl-
 phenyl]- or -NH-;
- n a number from 0 to 4;
- Cyc1 a 3 to 7 membered saturated, partially saturated or
 unsaturated ring, where 1 C atom may be replaced by
 O, N or S;
- R7, R8, R9 hydrogen, F, Cl, Br, I, OH, CF₃, NO₂, CN, COOH,
 COO(C₁-C₆)-alkyl, CO(C₁-C₄)-alkyl, CONH₂,
 CONH(C₁-C₆)-alkyl, CON[(C₁-C₆)-alkyl]₂, (C₁-C₆)-
 alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₁-C₆)-alkoxy,

(C₁-C₆)-alkyl-OH, (C₁-C₆)-alkoxy-(C₁-C₆)-alkyl, it being possible for one, more than one or all hydrogen(s) in the alkyl radicals to be replaced by fluorine;

5 SO₂-NH₂, SO₂NH(C₁-C₆)-alkyl, SO₂N[(C₁-C₆)-alkyl]₂,
 S-(C₁-C₆)-alkyl, S-(CH₂)_o-phenyl, SO-(C₁-C₆)-alkyl,
 SO-(CH₂)_o-phenyl, SO₂-(C₁-C₆)-alkyl,
 SO₂-(CH₂)_o-phenyl, where o can be 0-6, and the
 10 phenyl radical may be substituted up to twice by F, Cl,
 Br, OH, CF₃, NO₂, CN, OCF₃, O-(C₁-C₆)-alkyl,
 (C₁-C₆)-alkyl, NH₂;
 NH₂, NH-(C₁-C₆)-alkyl, N[(C₁-C₆)-alkyl]₂, NH(C₁-C₇)-
 acyl, phenyl, O-(CH₂)_o-phenyl, where o can be 0-6,
 15 where the phenyl ring may be substituted one to 3
 times by F, Cl, Br, I, OH, CF₃, NO₂, CN, OCF₃,
 (C₁-C₈)-alkoxy, (C₁-C₆)-alkyl, NH₂, NH(C₁-C₆)-alkyl,
 N[(C₁-C₆)-alkyl]₂, SO₂-CH₃, COOH, COO-(C₁-C₆)-
 alkyl, CONH₂;

or

20 R8 and R9 together with the C atoms carrying them a 5 to
 7 membered, saturated, partially or completely
 unsaturated ring Cyc2, it being possible for 1 or 2
 C atom(s) in the ring also to be replaced by N, O or S,
 and Cyc2 may optionally be substituted by (C₁-C₆)-
 25 alkyl, (C₂-C₅)-alkenyl, (C₂-C₅)-alkynyl, where in each
 case one CH₂ group may be replaced by O, or
 substituted by H, F, Cl, OH, CF₃, NO₂, CN,
 COO-(C₁-C₄)-alkyl, CONH₂, CONH(C₁-C₄)-alkyl,
 OCF₃;

30

and the pharmaceutically acceptable salts thereof.

2. A compound of the formula I as claimed in claim 1, in which the meanings are

35

R1, R2 OH, F or H or R1 and R2 = F, where one of the radicals R1, R2 must be F;

	R3	OH;
	A	O or NH;
5	X	S or optionally R6-substituted N, where Y must be CH when X is S;
	Y	CH or N;
10	m	a number 1 or 2;
15	R4, R5	hydrogen, F, Cl, Br, I, OH, CF ₃ , NO ₂ , CN, COOH, CO(C ₁ -C ₆)-alkyl, COO(C ₁ -C ₆)-alkyl, CONH ₂ , CONH(C ₁ -C ₆)-alkyl, CON[(C ₁ -C ₆)-alkyl] ₂ , (C ₁ -C ₆)-alkyl, (C ₂ -C ₆)-alkenyl, (C ₂ -C ₆)-alkynyl, (C ₁ -C ₆)-alkoxy, HO(C ₁ -C ₆)-alkyl, (C ₁ -C ₆)-alkoxy-(C ₁ -C ₆)-alkyl, phenyl, benzyl, SO-(C ₁ -C ₆)-alkyl, it being possible for one, more than one or all hydrogen(s) in the alkyl radicals to be replaced by fluorine; or
20		when X is S together with the C atoms carrying them phenyl;
25	R ⁶	H, (C ₁ -C ₆)-alkyl, (C ₁ -C ₆)-alkenyl, (C ₃ -C ₆)-cycloalkyl, or phenyl that may optionally be substituted by halogen or (C ₁ -C ₄)-alkyl;
30	B	(C ₀ -C ₁₅)-alkanediyl, where one or more C atom(s) in the alkanediyl radical may be replaced independently of one another by -O-, -(C=O)-, -CH=CH-, -C≡C-, -S-, -CH(OH)-, -CHF-, -CF ₂ -, -(S=O)-, -(SO ₂)-, -N((C ₁ -C ₆)-alkyl)-, -N((C ₁ -C ₆)-alkyl-phenyl)- or -NH-;
	n	a number 2 or 3;
35	Cyc1	a 3 to 7 membered saturated, partially saturated or unsaturated ring, where 1 C atom may be replaced by O, N or S;
	R7, R8, R9	hydrogen, F, Cl, Br, I, OH, CF ₃ , NO ₂ , CN, COOH,

- COO(C₁-C₆)-alkyl, CO(C₁-C₄)-alkyl, CONH₂,
 CONH(C₁-C₆)-alkyl, CON[(C₁-C₆)-alkyl]₂, (C₁-C₆)-
 alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₁-C₈)-alkoxy,
 (C₁-C₆)-alkyl-OH, (C₁-C₆)-alkoxy-(C₁-C₆)-alkyl,
 5 SO-(C₁-C₆)-alkyl, it being possible for one, more than
 one or all hydrogen(s) in the alkyl radicals to be
 replaced by fluorine;
 or
 R8 and R9 together with the C atoms carrying them a 5 to
 10 7 membered, saturated, partially or completely
 unsaturated ring Cyc2, where 1 or 2 C atom(s) in the
 ring may also be replaced by N, O or S, and Cyc2 may
 optionally be substituted by (C₁-C₆)-alkyl, (C₂-C₅)-
 alkenyl, (C₂-C₅)-alkynyl, where in each case one CH₂
 15 group may be replaced by O, or substituted by H, F,
 Cl, OH, CF₃, NO₂, CN, COO(C₁-C₄)-alkyl, CONH₂,
 CONH(C₁-C₄)-alkyl, OCF₃.
3. A compound of the formula I as claimed in claims 1 or 2, in which
 20 the sugar residues are beta(β)-linked and the stereochemistry in the
 2- and 5-position of the sugar residue has the gluco configuration.
4. A compound of the formula I as claimed in claims 1 to 3, in which
- 25 R1, R2 are OH, F or H or R1 and R2 = F, where one of the
 radicals R1, R2 must be F;
- R3 is OH;
- 30 A is O;
- X S or optionally R6-substituted N, where Y must be CH
 when X is S;
- 35 Y CH or N;
- m a number 1;
- R4, R5 are hydrogen, OH, (C₁-C₅)-alkyl, (C₁-C₄)-alkoxy,

- HO-(C₁-C₄)-alkyl, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, F, Cl, CF₃, OCF₃, OCH₂CF₃ (C₁-C₄)-alkyl-CF₂-, phenyl, benzyl, (C₂-C₄)-alkenyl, (C₂-C₄)-alkynyl, COO(C₁-C₄)-alkyl; or
- 5 when X is S together with the C atoms carrying them phenyl;
- R⁶ H, (C₁-C₆)-alkyl, (C₁-C₆)-alkenyl, (C₃-C₆)-cycloalkyl, or phenyl that may optionally be substituted by halogen or (C₁-C₄)-alkyl;
- 10
- B is (C₁-C₄)-alkanediyl, where one CH₂ group may also be replaced by -(C=O)-, -CH(OH)-, -CO-NH-, -CHF-, -CF₂-, -O-;
- 15
- n is a number 2 or 3;
- Cyc1 is unsaturated 5- or 6-membered ring, where 1 C atom may be replaced by O, N or S;
- 20
- R₇, R₈, R₉ are hydrogen, (C₁-C₄)-alkyl, (C₁-C₈)-alkoxy, OCF₃, OCH₂CF₃, OH, (C₁-C₄)-alkyl-OH, (C₁-C₄)-alkoxy-(C₁-C₄)-alkyl, or
- 25
- R₈ and R₉ together are -CH=CH-O-, -CH=CH-S-, -O-(CH₂)_p-O-, with p = 1 or 2, and
- R₇ is hydrogen.
- 30 5. A compound of the formula I as claimed in claims 1 to 4, in which
- R₁ is F and R₂ is H or
- R₁ is H and R₂ is F;
- 35
- R₃ is OH;
- A is O;
- X S or optionally R₆-substituted N, where Y must be CH

when X is S;

- | | | |
|----|------------|--|
| | Y | CH or N; |
| 5 | m | a number 1; |
| | R4, R5 | are hydrogen, OH, CF ₃ , (C ₁ -C ₃)-alkyl, or when X is S together with the C atoms carrying them phenyl; |
| 10 | R6 | H, (C ₁ -C ₄)-alkyl or phenyl; |
| | B | is -CH ₂ -, -C ₂ H ₄ -, -C ₃ H ₆ -, -CO-NH-CH ₂ - or -CO-CH ₂ -CH ₂ -; |
| 15 | n | is a number 2 or 3; |
| | Cyc1 | is unsaturated 6-membered ring, where 1 C atom may be replaced by N; |
| 20 | R7, R8, R9 | are hydrogen, (C ₁ -C ₄)-alkyl, (C ₁ -C ₇)-alkoxy, OCF ₃ or |
| | R8 and R9 | together are -CH=CH-O-, -O-(CH ₂) _p -O-, with p = 1 or 2, and |
| 25 | R7 | is hydrogen. |

6. A compound of the formula I as claimed in claims 1 to 5, in which

- | | | |
|----|----|---|
| | R1 | is F and R2 is H or |
| 30 | R1 | is H and R2 is F; |
| | R3 | is OH; |
| | A | is O; |
| 35 | X | S or optionally R6-substituted N, where Y must be CH when X is S; |
| | Y | CH or N; |

- m a number 1;
- 5 R4 is hydrogen, methyl or CF₃;
- R5 hydrogen or
- 10 R4 and R5 when X is S together with the C atoms carrying them phenyl;
- R6 H, (C₁-C₄)-alkyl or phenyl;
- B is -CH₂-, -CO-CH₂-CH₂- or -CO-NH-CH₂-;
- 15 n is a number 3;
- Cyc1 is unsaturated 6-membered ring;
- 20 R7, R8, R9 are hydrogen or methoxy.
7. A medicament comprising one or more of the compounds as claimed in one or more of claims 1 to 6.
8. A medicament comprising one or more of the compounds as
25 claimed in one or more of claims 1 to 6 and one or more blood glucose-lowering active ingredients.
9. The use of the compounds as claimed in one or more of claims 1 to 6 for producing a medicament for the treatment of type 1 and type 2
30 diabetes.
10. The use of the compounds as claimed in one or more of claims 1 to 6 for producing a medicament for lowering blood glucose.
- 35 11. The use of the compounds as claimed in one or more of claims 1 to 6 in combination with at least one other blood glucose-lowering active ingredient for producing a medicament for the treatment of type 1 and type 2 diabetes.

12. The use of the compounds as claimed in one or more of claims 1 to 6 in combination with at least one other blood glucose-lowering active ingredient for producing a medicament for lowering blood glucose.

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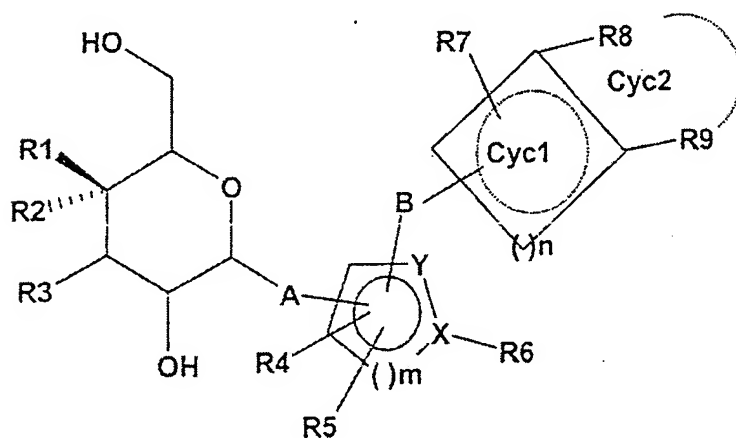
13. A process for producing a medicament comprising one or more of the compounds as claimed in one or more of claims 1 to 6, which comprises mixing the active ingredient with a pharmaceutically suitable carrier and converting this mixture into a form suitable for administration.

10

Abstract

Novel heterocyclic fluoroglycoside derivatives, medicaments containing these compounds, and the use thereof

The invention relates to substituted heterocyclic fluoroglycoside derivatives of the formula I



in which the radicals have the stated meanings, and their physiologically tolerated salts and process for their preparation. The compounds are suitable for example as antidiabetics.